UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

NYCOMED US INC.,

Plaintiff,

v.

PERRIGO ISRAEL PHARMACEUTICALS, LTD., AND PERRIGO COMPANY

Defendants.

Civil Action No. CV09- 5123

BLOOM, M.J. GLEESON, J.

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Nycomed US Inc. ("Nycomed" or "Plaintiff"), by its attorneys Kramer Levin Naftalis & Frankel LLP, for its Complaint against Perrigo Israel Pharmaceuticals, Ltd. and Perrigo Company (collectively "Perrigo") for patent infringement alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement of United States Patent No. 7,300,669 (the " '669 Patent"), arising under the food and drug and patent laws of the United States, Titles 21 and 35, respectively. This action relates to the Abbreviated New Drug Application No. 91-553 ("Perrigo's ANDA" or "ANDA") filed by Perrigo with the United States Food and Drug Administration ("FDA") for approval to market a generic copy of Nycomed's Cutivate® Fluticasone Lotion 0.05% drug product ("Cutivate® Lotion") covered by the '669 Patent.

THE PARTIES, JURISDICTION AND VENUE

2. Nycomed is a company organized and existing under the laws of the State of New York with its principal place of business at 60 Baylis Road, Melville, NY 11747-0103.

3. On information and belief, Defendant Perrigo Israel Pharmaceuticals, Ltd. is a company organized and existing under the laws of Israel, having a principal place of business at 29 Lehi Street, Bnei Brak 51200, Israel.

4. On information and belief, Defendant Perrigo Company is a company organized and existing under the laws of the State of Michigan, having a principal place of business at 515 Eastern Avenue, Allegan, Michigan, 49010.

5. On information and belief, Perrigo Israel Pharmaceuticals, Ltd. was formerly known as Agis Industries Limited. On information and belief, Perrigo Company purchased Agis Industries Limited in or around March 2005.

6. On information and belief, Perrigo Israel Pharmaceuticals, Ltd. is a wholly owned subsidiary of Perrigo Company.

7. On information and belief, Perrigo Israel Pharmaceuticals, Ltd. is an agent and/or alter ego of Perrigo Company.

8. On information and belief, Perrigo Israel Pharmaceuticals, Ltd. is under the direction, control and/or influence of Perrigo Company, both generally and with respect to the particular acts and conduct alleged in this Complaint.

9. On information and belief, Perrigo Company conducts operations through Perrigo Israel Pharmaceuticals, Ltd.

10. On information and belief, Perrigo is in the business of developing and manufacturing drug products for use and sale in the United States including in the State of New York and in this judicial district.

11. On information and belief, Perrigo conducts business and sells various drug products in the United States including in the State of New York and in this judicial district.

12. On information and belief, Perrigo has maintained continuous and systematic contacts with the State of New York and in this judicial district.

13. This Court has personal jurisdiction over Perrigo.

14. Perrigo has filed ANDA No. 91-553 with the purpose of obtaining the FDA's approval to market a proposed product that is a generic copy of Nycomed's Cutivate® Lotion before the expiration of Nycomed's '669 Patent. This ANDA creates a justiciable controversy between Nycomed and Perrigo with respect to the subject matter of Perrigo's ANDA, Perrigo's proposed product and the '669 Patent.

15. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), 35 U.S.C. § 271 and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

16. Venue is proper in this District under 28 U.S.C. §§ 1391 and 1400(b).

FACTUAL BACKGROUND

The ANDA Process

17. The Federal Food, Drug, and Cosmetic Act ("FFDCA") requires that before a drug manufacturer can market a new drug, it must submit a New Drug Application ("NDA") to the FDA for approval pursuant to section 505(b) of the Federal Food, Drug, and Cosmetics Act ("FFDCA"), 21 U.S.C. § 355(b). In addition to extensive testing and safety information concerning the drug, the manufacturer must also submit the patent number and expiration date of any patent that claims the drug or a method of using the drug with respect to which a claim of patent infringement could reasonably be asserted. 21 U.S.C. § 355(b)(1)(G).

18. Once the NDA is approved, the FDA lists this patent information with the approved drug in its *Approved Drug Products with Therapeutic Equivalence Evaluations*

publication, commonly known as the "Orange Book." *See* 21 U.S.C. §§ 355(b)(1). The FDA also maintains an electronic version of the Orange Book at www.fda.gov/cder/ob/.

19. In 1984 Congress adopted the Drug Price Competition and Patent Term Restoration Act, commonly known as the "Hatch-Waxman Act." This statute amended the FFDCA to provide for an ANDA, allowing manufacturers to obtain FDA approval for generic versions of previously approved drugs without having to repeat the extensive testing required for a new drug application, as long as certain requirements were met. *See* 21 U.S.C. § 355(j).

20. When submitting an ANDA to the FDA, the generic manufacturer must make one of the following four certifications with respect to each of the patents listed in the Orange Book for the drug for which the applicant seeks approval: (1) that no patent information has been filed (a "Paragraph I" certification), (2) that the patent has expired (a "Paragraph II" certification), (3) that the patent will expire on a specific date (a "Paragraph III" certification), or (4) that the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted" (a "Paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

21. If a generic drug applicant makes a Paragraph IV certification in its ANDA, the Hatch-Waxman Act requires that the applicant give notice to the patent owner ("Notice Letter"). In addition, in that Notice Letter, the ANDA applicant is required to provide the patent owner with a "detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv)(II).

22. The intended purpose of a Notice Letter is to inform a patentee of the basis for a Paragraph IV certification so that a patentee may determine, as permitted under the patent act, whether to commence an action for infringement of an Orange Brook listed patent or to understand that such an action would not be justified under the patent act.

Nycomed's Cutivate® Lotion And '669 Patent

23. Nycomed is the owner of the '669 Patent.

24. The '669 Patent, entitled "Fluticasone Lotion Having Improved Vasoconstrictor Activity," was duly and legally issued on November 27, 2007 to inventors Gordon Dow et al., by the United States Patent and Trademark Office. A copy of the '669 Patent is attached hereto as **Exhibit A**. The claims of the '669 Patent are directed to, *inter alia*, topical lotions containing fluticasone.

25. Nycomed is the owner of NDA No. 21-152, which the FDA approved pursuant to section 505(b) of the FFDCA, 21 U.S.C. § 355(b). This NDA is directed to Cutivate® Lotion, a topical prescription medication sold on the market and used to treat a variety of dermatological conditions such as eczema.

26. Nycomed is also the owner, marketer and seller of Cutivate® Lotion.

27. Nycomed's '669 Patent claims cover Nycomed's Cutivate® Lotion.

28. The FDA lists the '669 Patent with Nycomed's Cutivate® Lotion in the Orange Book.

Perrigo's ANDA And Notice Letter

29. On or about October 9, 2009, Perrigo sent Nycomed a Notice Letter stating, among other things, that Perrigo had submitted ANDA No. 91-553 to the FDA pursuant to 21 U.S.C. § 355 (j) seeking approval of Perrigo's proposed drug product Fluticasone Propionate Lotion 0.05% ("Perrigo's Lotion") as a copy of Nycomed's Cutivate® Lotion.

30. Perrigo's Notice Letter demonstrates that Perrigo seeks approval to "engage in the commercial manufacture, use, sale or importation of" a copy of Nycomed's Cutivate® Lotion prior to the expiration date of the '669 Patent.

31. Perrigo's Notice Letter states that Perrigo's ANDA contains a Paragraph IV certification with respect to the '669 Patent.

32. Perrigo's Notice Letter does not assert any cognizable or prima facie grounds of noninfringement, invalidity or unenforceability.

COUNT ONE: DIRECT INFRINGEMENT

33. Plaintiff alleges the paragraphs set forth above as if fully set forth herein.

34. Pursuant to 35 U.S.C. § 271(e)(2)(A), Perrigo has committed an act of infringement of the '669 Patent by filing an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Perrigo's generic copy of Nycomed's Cutivate® Lotion prior to expiration of Nycomed's '669 Patent. This Court has subject matter jurisdiction with respect to this action to declare Nycomed's rights under the '669 Patent.

35. Plaintiff is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Perrigo's ANDA be a date that is not earlier than the expiration date for the last to expire of the '669 Patent or any other Patent listed in the Orange Book for Cutivate® Lotion.

36. Plaintiff is further entitled to a declaration that, if Perrigo commercially manufactures, uses, offers for sale or sells Perrigo's generic copy of Cutivate® Lotion within the United States, imports Perrigo's generic copy of Cutivate® Lotion into the United States, or induces or contributes to such conduct, Perrigo would further infringe the '669 Patent under 35 U.S.C. § 271(a), (b) and/or (c).

37. Plaintiff will be irreparably harmed by Perrigo's infringing activities unless those activities are enjoined by this Court. Plaintiff does not have an adequate remedy at law.

COUNT TWO: INDIRECT INFRINGEMENT

38. Plaintiff repeats and realleges the allegations of the paragraphs set forth above as if fully set forth herein.

39. Perrigo's actual commercial manufacture, importation, use, offer for sale or sale of Perrigo's Lotion prior to the expiration of the '699 Patent is contributory infringement and/or active inducement of infringement by others of the '699 Patent under 35 U.S.C. § 271.

40. Perrigo Company, is jointly and severally liable with Perrigo Israel Pharmaceuticals, Ltd. for this indirect infringement of the '669 Patent. This is so, because upon information and belief, Perrigo Company will direct, participate in, contribute to, aid and abet Perrigo Israel Pharmaceuticals, Ltd.'s acts of manufacturing, importing, using, offering for sale, and selling Perrigo's Lotion prior to the expiration of the '669 Patent.

RELIEF SOUGHT

WHEREFORE, Plaintiff requests:

A) A judgment declaring the '669 Patent is valid and enforceable;

B) A judgment declaring that Perrigo has infringed, and that Perrigo's making, using, selling, offering to sell or importing Perrigo's Lotion will infringe, the '669 Patent;

C) An Order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Perrigo's ANDA No. 91-553 be a date that is not earlier than the expiration date of the '669 Patent, including any extensions of the patent term and/or exclusivities relating to Nycomed's Cutivate® Lotion;

D) A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) permanently enjoining Perrigo and its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from commercial manufacture, use, offer to sell, or sale within

the United States or importation into the United States of Perrigo's Lotion or any other product that infringes, induces or contributes to the infringement of the '669 Patent prior to the expiration date of the '669 Patent, including any extensions of the patent term and/or exclusivities relating to Nycomed's Cutivate® Lotion;

E) A judgment of damages, should Perrigo engage in commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of Perrigo's Lotion or any other product that infringes, induces or contributes to the infringement of the '669 Patent prior to the expiration date of the '669 Patent, including any extensions of the patent term and/or exclusivities relating to Nycomed's Cutivate® Lotion, resulting from such infringing activities, increased to treble the amount found or assessed together with interest;

F) A judgment declaring that this is an exceptional case entitling Nycomed to an award of its reasonable attorney's fees, together with interest, and costs of the action, pursuant to 35 U.S.C. § 285;

G) Costs and expenses in the action; and

H) Such other and further relief as the Court may deem just and proper.

Dated: November 20, 2009

Respectfully submitted,

By: 

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(12) **United States Patent**
Dow et al.

(10) **Patent No.: US 7,300,669 B2**
(45) **Date of Patent: Nov. 27, 2007**

(54) **FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY**

(75) Inventors: **Gordon J. Dow**, Petaluma, CA (US); **Keith Arthur Johnson**, Durham, NC (US); **Frances Furr Kelly**, Durham, NC (US); **Robert William Lathrop**, Fort Collins, CO (US); **Rukmini Rajagopalan**, Durham, NC (US)

(73) Assignee: **Altana Inc.**, Melville, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 530 days.

(21) Appl. No.: **10/800,840**

(22) Filed: **Mar. 15, 2004**

(65) **Prior Publication Data**

US 2004/0176342 A1 Sep. 9, 2004

Related U.S. Application Data

(63) Continuation of application No. 09/830,037, filed as application No. PCT/GB99/03472 on Oct. 20, 1999, now abandoned.

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 31/56 (2006.01)

(52) **U.S. Cl.** **424/484**; 424/485; 424/486; 514/177

(58) **Field of Classification Search** 514/177; 424/484, 485, 486

See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

19 Claims, No Drawings

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

This application is a continuation of U.S. Ser. No. 09/830,037 filed 20 Apr. 2001, now abandoned which is a §371 national stage filing of PCT/GB99/03472 filed 20 Oct. 1999.

FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt. %, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt. % of a C_{14}-C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt. % of at least one skin conditioning agent; about 5.0 to 15.0 wt. % of propylene glycol; up to about 10.0 wt. % mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt. %; a C_{14}-C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt. %; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt. %; at least one surfactant in an amount of about 0.25 to 3.0 wt. %; propylene glycol in an amount of from about 7.0 to 12.0 wt. %; up to about 10 wt. % mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroid-responsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the steps or acts of providing a lotion including about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt. % of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt. % of one or more skin conditioning agents; about 5.0 to 15.0 wt. % of propylene glycol; up to about 10.0 wt. % of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40° C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt. % preferably 0.005 to 0.5 wt. %, and more preferably about 0.005 to about 0.1 wt. %. The C_{14}-C_{20} fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14}-C_{20} fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt. %, preferably about 3.0 to 7.0 wt. %, and more preferably about 4.0 to 6.0 wt. %.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt. %, preferably about 1.0 to 3.0 wt. %, and more preferably about 1.0 to 2.0 wt. %. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about

5.0 wt. %, preferably about 0.5 to 3.0 wt. % and more preferably about 1.0 to 2.0 wt. % of the lotion composition.

At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14}-C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt. %, preferably about 0.5 to 2.0 wt. %, and more preferably about 0.75 to 1.5 wt. %.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt. %. The lotion may also contain up to about 5.0 wt. % or up to about 2.0 wt. % skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt. %, preferably about 7.0 to 12.0 wt. % and more preferably 9.0 to 11.0 wt. %.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25° C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80° C.) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

A topical 0.05 wt. % fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Cetostearyl alcohol, NF	5.00
Isopropyl myristate, NF	1.00
Dimethicone 360, NF	1.00
Cetomacrogol 1000, BP	1.00
Propylene glycol, USP	10.00
Imidurea, NF	0.30
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric acid (anhydrous), USP	0.05
Sodium citrate, USP	0.08
Purified water, USP	balance

Example 2

A topical 0.05 wt. % fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	balance

Example 3

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	3.0
Isopropyl myristate	3.0
Ceteth-20	0.75
Propylene Glycol	0.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 4

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.25

-continued

Ingredient	(wt. %)
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 6

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	5.0
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0

-continued

Ingredient	(wt. %)
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 8

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 9

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	4.7
Isopropyl myristate	3.75
Dimethicone	3.75
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.01
Stearyl Alcohol	5.0
Isopropyl myristate	3.0
Dimethicone	3.0
Ceteth-20	0.75
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Cetyl Alcohol	7.0
Mineral Oil	2.0
Isopropyl myristate	2.0
Dimethicone	2.0
Cetomacrogol 1000	1.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 14

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Stearyl Alcohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 15

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Cetostearyl Alcohol	5.0
Mineral Oil	2.5
Dimethicone	1.0
Tween ® 40	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 16

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25
Mineral Oil	5.0
Brig ® 78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 17

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.0
Isopropyl myristate	5.0
Cetomacrogol 1000	0.5

-continued

Ingredient	(wt. %)
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 18

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608 (1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm^2 area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

TABLE 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE ® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

*Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

TABLE 2

		Responder Population		
Treatment	Potency	2 hour score	AUC	Avg. mean blanching
TEMOVATE ™	High	2.7	36.6	2.0
ELOCON ™	High	2.2	33.4	1.8
Fluticasone lotion (0.05%)	Mid to High	2.1	26.7	1.5
CUTIVATE ™ Cream	Mid	1.8	21.4	1.2
HYTONE ™ Lotion	Low	0.8	9.5	0.6

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005,

FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

Ingredient	(wt. %)
fluticasone propionate (micronized)	0.05
cetostearyl alcohol, NF	5.0
isopropyl myristate, NF	1.0
dimethicone 360, NF	1.0
polyoxyethylene (20) cetostearyl ether, NF	1.0
propylene glycol, USP	10.0
imidurea, NF	0.14
methylparaben, NF	0.17
propylparaben, NF	0.06
citric acid (hydrous), USP	0.05
sodium citrate, USP	0.08
purified water, USP	balance (also QSAD)

TABLE 3

Study	Diagnosis	Application	No. subjects	Outcome Good to cleared (%)
FPL30003	Atopic Dermatitis	QD for up to 4 weeks	FPL (110) Veh. (110)	FPL (78%)* Veh. (33%)
FPL30004	Atopic Dermatitis	QD for up to 4 weeks	FPL (111) Veh. (107)	FPL (68%)* Veh. (28%)

*subjects showing >50% clearing of lesions
"Veh." is vehicle only formulation

The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin ($ACTH_{1-29}$) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

TABLE 4

Cortisol responses - plasma levels = 18 ug/dL indicate suppression

Study	Preparation	Adrenal Responsiveness, # suppressed/total
FPL10005	Lotion	0/42

These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin ($ACTH_{1-29}$) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion. These results were unexpectedly superior based on potency estimates from the VC Assay.

Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N=110 treated with fluticasone); FPL30004; N=111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATE™ Cream and (2) that the side effects would reflect those observed for CUTIVATE™ Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

We claim:

1. A topical lotion, comprising:
about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof;
about 4.0 to 6.0 wt. % of a C_{14}-C_{20} fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt. % of at least one first skin conditioning agent;
about 5.0 to 15.0 wt. % propylene glycol; and
the balance in water;
wherein the lotion is free of mineral oil and white soft paraffin, and
wherein the lotion causes more vasoconstriction when applied to living human skin than does application of a cream containing mineral oil or soft white paraffin, or both, the cream containing the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof.

2. The lotion of claim **1** further comprising about 0.25 to 3.0 wt. % of at least one surfactant.

3. The lotion of claim **1** further comprising about 0.5 to 2.0 wt. % of at least one surfactant.

4. The lotion of claim **1** further comprising dimethicone in an amount up to about 5.0 wt. %.

5. The lotion of claim **4** further comprising about 0.5 to 3.0 wt. % of dimethicone.

6. The lotion of claim **4** further comprising about 1.0 to 2.0 wt. % of dimethicone.

7. The lotion of claim **5** wherein said C_{14}-C_{20} fatty alcohol or mixtures thereof is cetostearyl alcohol.

8. The lotion of claim **7** wherein said first skin conditioning agent is isopropyl myristate.

9. The lotion of claim **8** further comprising about 0.25 to 3.0 wt. % of at least one surfactant.

10. The lotion of claim **8** further comprising about 0.5 to 2.0 wt. % of at least one surfactant.

11. The lotion of claim **10** wherein said surfactant is Cetomacrogol.

12. The lotion of claim **11** further comprising one or more buffers.

13. The lotion of claim **12** further comprising one or more preservatives.

14. The lotion of claim **13** wherein said fluticasone, or a pharmaceutically acceptable salt or ester thereof is fluticasone propionate.

15. The lotion of claim **14** wherein said one or more buffer is selected from the group consisting of: sodium citrate and citric acid.

16. The lotion of claim **15** wherein said one or more preservative is selected from the group consisting of: imidurea, methylparaben, and propylparaben.

17. A method of treating a skin condition treatable by fluticasone, comprising topically administering to a patient in need thereof a lotion according to claim **14**.

18. The method of claim **15** wherein said skin condition is selected from the group consisting of: corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis.

19. A topical lotion, comprising:

about 0.05 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof;

about 4.0 to 6.0 wt. % of cetostearyl alcohol;

about 1.0 to 2.0 wt. % of isopropyl myristate;

about 5.0 to 15.0 wt. % propylene glycol;

about 0.5 to 3.0 wt. % of dimethicone;

about 0.25 to 3.0 wt. % of at least one surfactant; and

the balance in water;

wherein the lotion is free of mineral oil and white soft paraffin, and

wherein the lotion causes more vasoconstriction when applied to living human skin than does application of a cream containing mineral oil or soft white paraffin, or both, the cream containing the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof.

* * * * *